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A Review of Codeine Addiction and a Study of the Minimum Cough-Relieving Dose

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THE ABUSE OF CODEINE

A Review of Codeine Addiction and a Study of the Minimum Cough-Relieving Dose *

By LOWREY F. DAVENPORT, M. D., *Attending Specialist, United States Public Health Service, U. S. Marine Hospital, Boston (Chelsea), Mass.*

INTRODUCTION

Codeine is the generally accepted sedative for the control of cough, but its addiction liability has not been fully appreciated. In Canada, where until recently no restrictions were placed on the sale of codeine, addiction to the drug has become a grave problem. The per capita consumption of codeine in Canada is 3½ times the per capita consumption in the United States and 10 times that in Great Britain (*1*). In the United States, Treadway (*2*) reports variations in per capita consumption by States ranging from less than $^{36}/_{100}$ grain to more than 1 and $^{44}/_{100}$ grains, which variation can be explained only through some misuse of the drug.

Hatcher (*3*) states that in some cases $^{1}/_{30}$ grain (0.002 g) of morphine will relieve cough. Since we were able to confirm this among our own patients, we were led to study the minimum similarly effective dose of codeine.

OFFICIAL DOSAGE

Codeine was discovered in 1832 by Robiquet and was placed in the Pharmacopoeia about 1880. The dose was not given, but it was reported in 1883 (*4*) that S. Weir Mitchell took 5 grains (0.3 g) without toxic effects other than "nausea, slight giddiness, cerebral heaviness, and a slight acceleration of pulse." In 1894 codeine was recommended for cancer, diabetes, and "painful disease of the abdomen such as obstruction, organic disease, enteralgia" (*5*). In the seventeenth edition of the U. S. Dispensatory a beginning dose of less than 1 grain was recommended, with rapid increase "until some (sic) symptoms are produced."

Even now there is considerable confusion as to the cough-relieving dose of codeine. The Harrison Narcotic Act exempts preparations containing no more than one-quarter grain (0.015 g) of morphine or 1

* From the Middlesex County Sanatorium, Waltham, Mass., and Department of Medicine, Harvard Medical School. This study was initiated by the Committee on Drug Addiction of the National Research Council through the cooperation of the United States Public Health Service and the Massachusetts Department of Public Health.

grain (0.060 g) of codeine per ounce. Most available cough sirups are prepared under this exemption. The average dose of such preparations contains not more than 1/32 grain (0.002 g) of morphine or 1/8 grain (0.008 g) of codeine. In changing from a cough sirup to tablet form, the narcotic dose is increased fourfold. Either the antitussic effect of the sirups is a delusion or the tablet dosage is needlessly large.

CODEINE ADDICTION

Codeine occurs in natural opium, though usually in small amounts (0.2 to 0.7 percent). Commercially, codeine is made by the methylation of morphine; and if it had been called by its chemical name, methyl morphine, its narcotic action would probably have demanded more attention. Because of the expense, the relative insolubility, and the definitely weaker action of codeine, addicts to this form of drug are numerically few as compared with the number of heroin or morphine addicts. This had led to a false sense of security that allowed Sollman (*6*) to state that "codeine deserves preference (in cough) since it produces the desired effect * * * without habit formation." Also Cushney (*7*) has said: "No tolerance is required for codeine." Bastedo (*8*) admitted having seen cases with codeine habit but believed the habit no worse than that due to the barbiturates. Watson (*9*), in 1922, found no cases of addiction among 700 replies from a questionnaire sent to physicians.

"A positive result outweighs one hundred negatives." This aphorism, current at birth-control clinics, might be similarly applied to the question of addiction. The letter of a former addict to the Vancouver Sun (*10*) warning the public of the dangers of codeine addiction carries more weight than the negative assurance of a dozen textbooks. The reported cases of known codeine addiction give incontrovertible evidence of the dangers of the drug. Table 1 lists 32 cases of codeine addiction. In addition to these detailed cases, Sharman (*11*), reporting the existing problem in Canada, referred to 34 known cases of codeine addiction in the hospitals of a single Province. Terry (*12*) in a survey of Detroit, found 83 addicts regularly using codeine and 420 "borderline" codeine addicts. The "borderline addicts" constitute the problem of codeine addiction, as these individuals will change to the more potent morphine or heroin as soon as the craving for a narcotic is recognized.

TABLE 1.—*Reported cases of codeine addiction*

Author	Number of cases
Pelz: Deut. Med. Wchnschr., **31**: 864 (1905)	1
Sollier, P.: Rev. de Méd. lég., **20**: 359 (1913)	1
Lambert, A.: Nelson Loose-Leaf Living Medicine, Thomas Nelson and Sons, **2**: Chapter on Intoxicants and Narcotics, p. III	17
Rougues de Fursac, J., and Monestier, M.: Ann. de Med. lég., **4**: 119 (1924)	1
Terry, C. E.: The opium problem, New York, Bureau of Social Hygiene, 1928, p. 321	2
Joel: Cited by Schwarz	1
Schwarz, H.: Deut. Med. Wchnschr., **56**: 8 (1930)	3
Heimann-Hatry, W.: Med. Klin., **26**: 1669 (1930)	1
Foley, H. T.: Pennsylvania Med. J., **36**: 44 (1932)	1
Slight, D.: Canad. Med. Assoc. J., **32**: 69 (1935)	3
Chodzko, W.: Bull. Office Internat. d'Hyg. pub., **27**: 2389 (1935)	1

Experimental evidence as to the potential addiction liability of codeine is in direct contradiction to the negative clinical data. Myers (*13*) and, later, Downs and Eddy (*14*) have shown that dogs habituated to morphine exhibit a cross tolerance for codeine. Himmelsbach (*15*) was able to support established morphine addiction through the substitution of codeine. It must be remembered that so dangerous a drug as heroin was for many years generally considered to be nonhabit forming (*16*). More recently the addiction quality of dilaudid caused a similar controversy (*17*).

DEVELOPMENT OF CODEINE ADDICTION

Treadway (*2*) believes the most important predisposing cause of addiction to be "an inherent mental or nervous instability." He further states that, among 1,225 addicts in whom the cause for addiction was known, 23 percent were due to previous use of drugs in medical treatment and 17 percent to self-treatment for the relief of pain. If, then, a "craving" for a narcotic drug is established in an emotionally unstable person by the legal use of codeine, the individual will attempt to satisfy this craving by illegal means. This viewpoint is stated emphatically by Terry (*12*) following the survey in Detroit:

> There was noted also a significant fact in following the chronology of a number of cases of addiction. Early in the year the drug taken by these cases was codeine in relatively small doses. Later the size of the prescriptions increased as well as their frequency, and morphine, heroin, or opium itself came to be substituted in ever increasing amounts.

The chronic addict is then reported as addicted to morphine or heroin rather than to codeine. This paucity of chronic codeine addicts in any statistical survey may be more readily understood by drawing an analogy between narcotic addiction and alcoholism. We might readily expect an emotionally unstable individual to develop a taste for alcohol from drinking vintage Burgundy; yet when such an individual realizes that his craving is for the alcohol itself, he will change to a more potent, less expensive preparation. Consequently, a tabular

summary of chronic alcoholics will reveal an infinitesimal number of addicts to vintage Burgundy as compared with village gin.

PLAN OF STUDY

In the present study advanced cases of pulmonary tuberculosis complaining of disturbing cough were used as test subjects. Tablets [1] identical in size and shape were used to facilitate change in drug and dosage without the knowledge of the patient. Daily observations were made by the nurse and the physician in charge. More important information was supplied by the patient through the use of a "diary sheet." Table 2 gives the tabular summary from a sample protocol.

TABLE 2.—*Comparative effect of changing drug and dosage* [1]

Changing—	Number reporting result as—			Number reporting duration of relief as—		
	Improved	Worse	No change	Increased	Decreased	No. change
Codeine 0.010 g to milk sugar	0	9	3	0	9	3
Milk sugar to morphine 0.005 g	9	0	3	9	0	3
Morphine 0.005 g to morphine 0.003 g	1	1	10	1	1	10
Morphine 0.002 g to codeine 0.010 g	2	2	10	2	1	11

[1] The discrepancy in the total number is the result of the loss of two patients from this series, one by death, and another, following a large hemorrhage, was excluded from the study.

Quite uniformly we were able to demonstrate satisfactory subjective relief from cough in the average patient by using doses of ⅙ grain (0.010 g) of codeine, repeated every 4 hours if indicated. The average duration of relief approximated that found in previous experience with larger doses, as shown in table 3.

TABLE 3.—*Average duration of relief*

Drug	Dose	Duration of relief
	Gram	*Hours*
Morphine	0.003	3⅓
Do	.005	4⅓
Codeine	.005	3⅓
Do	.010	4

Following the completion of this study we were convinced that our average tablet dose of codeine was unnecessarily large, and during the past year we have supplied the wards of the Middlesex County Sanatorium with codeine in ⅙ grain (0.010 g) tablets. The sanatorium staff of eight physicians from eight different medical schools was given a free hand in increasing the dosage of codeine from ⅙ grain (0.010 g) to ½ grain (0.030 g) when deemed desirable. Exclud-

[1] These tablets were manufactured through the kindness of Merck & Co., Rahway, N. J., from material supplied by the United States Public Health Service.

ing dying patients and those suffering from hemorrhage, the dosage was increased to ½ grain in 21 of an approximate total of 475 patients treated from July 1, 1937, to January 1, 1938. Only 3 of these 21 cases reported satisfactory relief from cough with the threefold increase in codeine dosage.

ADVANTAGES

Aside from diminishing the possibility of fostering addiction in the admittedly rare individual, there has been a direct financial saving to the institution. Without numerical correction for an increase of 150 beds to the sanatorium in May 1937, or for a calendar correction during the first quarter in 1937, when the larger doses were used, codeine consumption during 1936 and 1937 was as follows:

Codeine consumption

	⅛ grain	¼ grain	½ grain
1936	------	18,000	12,500
1937	19,215	3,000	5,000

The difference in cost of the several strengths has meant a saving of nearly $200 for the calendar year 1937; and corrected figures, if available, would show a saving of nearly 60 percent in 1937 as compared with 1936. Not only are we using smaller doses of codeine, but we are using codeine less frequently in the average case. This possibly means a better understanding of cough control; and if, as we believe, our patients have been just as comfortable as formerly, the intangible saving through avoiding the undesirable side actions of a narcotic has been incalculable.

CONTROL OF COUGH

Cough control through the use of narcotic drugs is unnecessary in the large majority of patients suffering from pulmonary tuberculosis. Rest of the diseased lung, either physiological through rest in bed, or mechanical, by means of surgical compression, is the most desirable means of decreasing cough. Many patients learn to suppress voluntarily the nonproductive cough. In our sanatorium population, which usually averages 60 percent of far-advanced cases, less than 17 percent regularly require antitussic drugs. The detailed figures as of December 31, 1937, are given in table 4.

TABLE 4.—*Number of patients in sanatorium, and number receiving codeine, Dec. 31, 1937*

	Number	Percent
Total number of patients	378	----------
Patients receiving codeine	64	16.9
Patients requiring but 1 dose	29	7.7
Patients requiring 2 doses	12	3.2
Patients requiring more than 2 doses	23	6.1

Of those receiving codeine, 5 patients were taking ½ grain (0.030 g) three times or more daily. One patient, a terminal case, has since died. Two were having severe hemoptyses, and in two the increased dosage was an unsuccessful attempt to control cough productive of more than 6 ounces of sputum in 24 hours.

We recognize three types of cough in prescribing for tuberculous patients: The moderately productive cough with sputum averaging less than 4 ounces in 24 hours; the profusely productive cough where the expectoration may amount to 1 pint or more; and the dry, irritative laryngeal cough.

A cough with moderate expectoration is well controlled with small doses of codeine. The medication may be needed only at bedtime, or the occasional case may require ⅛ grain (0.010 g) repeated every 4 hours.

The dry, nonproductive cough is usually associated with laryngeal irritation, and in the tuberculous case is associated with tuberculous involvement of the larynx itself. Codeine, and even morphine, in large doses is never wholly effective. The laryngeal irritation, whether acute or tuberculous, is best treated directly by topical applications of medicated oil. Advanced cases of laryngeal tuberculosis may be treated by spray with a local anesthetic, preferably one of the synthetic preparations.

The profusely productive cough is a necessary evil, as it cleans the air passages of secretions which might otherwise cause asphyxia. This type of cough can be prevented only by a narcotic dose which will cause a central depression. The physician should reserve such large narcotic doses only for the terminal case where a physiologically vital reflex may be sacrificed for the comfort of the dying patient.

The use of the larger doses of codeine or morphine among ambulatory patients is wholly unjustified. At the sanatorium we never allow physical exercise where medication is required for cough. The recumbent respiratory rate compared to that while walking is positive evidence that pharmacological sedation is less effective than physiological rest. The physician who ignores this fact is guilty of negligence. He violates the same physiological principle as the physician who prescribes a narcotic for relief of pain while allowing his patient to walk on a broken leg. Whether a broken lung, with cough, or a broken leg, with pain, the underlying principle is the same.

CONCLUSIONS

1. The addiction liability of codeine as used in routine medical practice is not fully recognized.

2. In the treatment of cough the accepted dosage of codeine is unnecessarily large.

3. In sanatorium practice the average patient will obtain relief from ⅙ grain (0.010 g) of codeine repeated every 4 hours as indicated.

4. Larger doses of codeine should be reserved for terminal cases and are never justified in ambulatory patients.

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